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5-HT1 receptor agonists for the treatment of L-DOPA-induced dyskinesia: From animal models to clinical investigation

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ABSTRACT

Appearance of dyskinesia represents the most problematic side effect during chronic L-DOPA treatment in parkinsonian patients, with serious consequences for the patient's quality of life. These side effects are generally attributed to dysregulation of dopamine (DA) transmission and maladaptive changes in the basal ganglia motor circuits.

To date, the NMDA receptor antagonist amantadine is the only drug used in patients to control dyskinesia, but with limited efficacy and side effects. Recent evidence in animal models of PD have demonstrated that L-DOPA-induced dyskinesia (LID) emerges as a consequence of abnormal release of striatal DA from the serotonin neurons, which causes a pulsatile stimulation of dopamine receptors. Accordingly, removal of serotonin innervation by 5,7-dihydroxytryptamine (5,7-DHT) administration or pharmacological silencing of serotonin neuron activity by 5-HT1A or 5-HT1B receptor agonists have been shown to suppress LID in 6-OHDA-lesioned rats, as well as in MPTP-treated monkeys.

Despite encouraging results have been obtained in pre-clinical models, clinical trials using 5-HT1A serotonin receptor agonists as anti-dyskinetic agents have been mostly disappointing. However, our pre-clinical data suggest that simultaneous activation of 5-HT1A and 5-HT1B receptors induced a potent synergistic effect on suppression of dyskinesia. Thus, clinical investigations employing a mixed 5-HT1A/1B receptor agonist have been recently initiated, and positive preliminary results have been reported.

In this review, we will discuss the recent experimental and clinical evidence supporting a potential therapeutic application of serotonin 5-HT1 receptor agonists in LID.

Contents

1. Introduction

Parkinson's disease (PD) is a chronic and progressive disorder characterized by degeneration of the nigrostriatal neuronal pathway leading to a loss of dopaminergic neurons and reduction of striatal dopamine (DA) levels.

The gold standard pharmacological treatment for PD is represented by oral administration of the DA precursor L-DOPA (L-3,4-dihydroxyphenylalanine), which alleviates most of the motor symptoms.

Although L-DOPA is initially well tolerated, with the progression of the disease, the therapeutic window of the drug narrows, leading to a reduction of the duration effect of each dose. Moreover, long-term DA replacement therapy with L-DOPA is associated with development of side effects in the majority of patients after a

Abbreviations: 6-OHDA, 6-hydroxydopamine; AIMs, Abnormal involuntary movements; DA, Dopamine; L-DOPA, L-3,4-dihydroxyphenylalanine; LID, L-DOPA-induced dyskinesia; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; PD, Partkinson's disease.

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variable number of years of drug administration, limiting the use of L-DOPA in advanced stages of the disease. These side effects include motor fluctuations, like wearing off, on–off, non-motor complications, as behavioural and cognitive changes, and motor complications including dystonia, chorea, and athetosis, collectively known as L-DOPA-induced dyskinesia (LID).

Alternative strategies to limit the motor complications consist in using subcutaneous or intraduodenal infusions of L-DOPA or apomorphine [1] or the use of deep brain stimulation in the subthalamic nucleus [2]; however, these approaches are invasive and expensive.

A lower risk of developing dyskinesia has been shown in patients treated with DA agonists that have relatively long half-lives, like ropinirole or pramipexole, or very long half-lives, like cabergoline [3,4]; nevertheless, when L-DOPA is added to the treatment patients develop dyskinesia.

These observations highlight a strong need for the development of new strategies to control dyskinesia.

To date, the only non-dopaminergic anti-dyskinetic drug used in patients is the glutamate antagonist amantadine [5]. However, this treatment is only moderately effective, shows side effects and its efficacy declines over time [6–8].

Although the use of animal models is leading to a better understanding of the pathophysiology of LID, the mechanisms involved in dyskinesia development are not fully understood and its treatment remains mainly symptomatic.

The rate of development of dyskinesia depends on several factors such as the level of nigrostriatal degeneration and the age of disease onset. Moreover, the gradual development and persistence of LID suggest that a brain synaptic plasticity is implicated in its pathophysiology [9].

Recent clinical and experimental findings indicate that, in addition to the alterations affecting the dopaminergic system, abnormalities in the neuronal activity of other neurotransmitter systems, within and outside the basal ganglia, are involved in the appearance of dyskinesia [10–12].

Accumulating evidence over the last few years have attributed a primary role to the serotonin system in the induction and expression of LID.

In fact, more recent studies have implicated raphestriatal serotonin neurons as a major source of striatal L-DOPA-derived DA in the parkinsonian brain, as they contain the enzymatic machinery responsible for decarboxylation of L-DOPA to DA, and for neurotransmitter storage into synaptic vesicles [13,14]. However, these neurons lack the DA transporter (DAT) and the D2 autoreceptors, and thus, they release DA in an unregulated manner, which leads to pulsatile stimulation of DA receptors, that is ultimately responsible for induction of the post-synaptic changes underlying LID [15–19].

In agreement with a serotonin-dependent production of L-DOPA-derived DA, it has been found, both in mice and rats, that administration of L-DOPA produces significant decrease in striatal serotonin tissue content [16,20], which can be explained with a competition between DA and serotonin for storage into serotonin synaptic vesicles.

2. Mechanisms of LID: evidence from animal models

A better understanding of the mechanisms underlying the appearance of dyskinesia has been achieved during recent years using animal models of LID. In fact, two available models of abnormal involuntary movements (AIMs), where administration of L-DOPA resemble peak-dose dyskinesia seen in patients, are represented by the 6-hydroxydopamine (6-OHDA)-lesioned rat and 1-methyl- 4-phenyl-1,2,3,6 tetrahydropyridine (MPTP)-treated monkey models [21,22].

Recent findings have indicated that both pre-synaptic and post-synaptic mechanisms affect induction and expression of dyskinesia. It has been demonstrated that LID is associated with plastic changes in post-synaptic neuronal targets in the striatum, including alterations in gene expression, and abnormal trafficking of DA D1 receptor, as well as of NMDA and AMPA glutamate receptor subunits [23–28].

Moreover, pre-synaptic compartments play an important role in the development of dyskinesia. The state of degeneration of the DA neurons probably represents the main risk factors for the appearance of dyskinesia. Indeed, in complete DA-lesioned animals, low doses of L-DOPA are sufficient to induced dyskinesias, which usually appear within few administrations of L-DOPA [16]. By contrast, higher doses of L-DOPA are required to induce significant dyskinesias when a partial dopaminergic lesion is established [29]. This effect can be attributed to the ability of the preserved DA terminals to prevent excessive post-synaptic DA receptor stimulation. In agreement, rats in which DA levels have been depleted by short hairpin RNA (leaving intact DA terminals), develop dyskinesias in response to apomorphine administration, but are fully resistant to LID development [29].

Large intermittent fluctuations in brain levels of DA have been classically attributed a prime causal role in LID [15,30], and are inhibited by a sufficiently preserved nigrostriatal DA innervation, as the one characterizing early stage of PD. However, as the disease progresses, the buffering capacity for the exogenous L-DOPA is gradually lost, and fluctuations in DA levels appear.

Recent studies in animal models of LID and PD patients have shown a reduced expression or dysfunction of the DA transporter (DAT) in residual nigrostriatal terminals [31,32], and a high density of serotonergic axon fibers in the striatum [33], suggesting that these events might be involved in the increase of extracellular DA levels and in DA fluctuations following L-DOPA administration.

An increasing body of experimental evidence suggests that DA released from the serotonin neurons (after L-DOPA administration) produces pro-dyskinetic effects. In agreement, it has been demonstrated that selective toxin lesion of the serotonin neurons by 5,7-DHT causes a reduction of L-DOPA-derived extracellular DA levels by about 80% in the striatum of complete DA-lesioned rats and near-to-full suppression of LID, while apomorphine-induced dyskinesia (which is not dependent on serotonin neurons to act on post-synaptic receptors) is not affected [16,17,34,35].

Furthermore, recent evidence has positively correlated the density of serotonin transporter (SERT) with the severity of LID in the striatum of both parkinsonian rats and monkeys, as well as in post-mortem tissue from PD patients, suggesting that the development of LID involves dysfunctional neuroplasticity of the 5-HT axonal fibers [33]. In line with these studies, it has recently been shown that serotonin transporter inhibition attenuates LID in hemi-parkinsonian rats [36].

These findings provide overwhelming evidence supporting an important role of serotonin neurons on LID, at least in animal models of PD.

3. 5-HT1 receptor agonists as anti-dyskinetic drugs: pre-clinical evidence

The serotonin system has several different types of receptors distributed in most of the brain areas, including the cortex, hippocampus, and basal ganglia. Among the most studied are the 5-HT1A and 5-HT1B autoreceptors. The 5-HT1A receptors are mainly located somatodendritically in the dorsal and median raphe nuclei, where they regulate the firing of the serotonergic neurons [37,38]. The 5-HT1B receptors, on the other hand, are more abundant at the terminal level in the areas innervated by the serotonin system, including the striatum, where they serve to